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EXAMINER
CROW, ROBERT THOMAS

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/510,107	OLSSON ET AL.	
	Examiner	Art Unit	
	Robert T. Crow	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 September 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 29 September 2009 has been entered.

Status of the Claims

2. This action is in response to Request for Continued Examination filed 3 June 2008 (with non-compliant claim amendments), the supplemental non-compliant amendment filed 19 June 2008, and the instant amendment filed 29 September 2008 in which no claims were amended, claims 1-6, 8, and 10-16 were canceled, and new claims 19-41 were added. All of the amendments have been thoroughly reviewed and entered.

The amendment to the specification filed 3 June 2008 is acknowledged and has been entered.

The previous rejections under 35 U.S.C. 103(a) not reiterated below are withdrawn in view of the amendments. Applicant's arguments have been thoroughly reviewed and are addressed following the rejections necessitated by the amendments.

The previous rejections under the judicially created doctrine of obviousness-type double patenting against the claims of copending Application No. 10/529,352 are withdrawn because the conflicting claims have been withdrawn from prosecution.

Claims 19-41 are under prosecution.

3. The following are new rejections necessitated by the amendments.

Claim Rejections - 35 USC § 112, First Paragraph

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 30, 32, 39 and 41 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. This is a new matter rejection. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

A. Claims 30 and 39 each recite the limitation “in which step c) is performed at a pH below 7” at the end of each of the claims. Original claim 14 and lines 20-25 on page 5 of the specification provide support for “step c) is performed at a pH below 7.” However, both recitations explicitly refer to an embodiment of "step c)" that is limited only to the polymerase extension reaction. Independent claims 19 and 33, upon which

claims 30 and 39 respectively depend, recite a “step c)” that also includes either photobleaching or cleavage of a cleavable link. A review of the specification yields no recitation of either photobleaching or cleavage of a cleavable link performed at a pH below 7. Thus, while the specification supports performing the polymerase reaction at a pH below 7, the specification does not support the additional performance of either the photobleaching or cleavage of a cleavable link to be performed at a pH below 7 as required by step)c of the instant claims. Therefore, the requirement that step c) as claimed be performed at a pH below 7 constitutes new matter.

B. Claims 32 and 41 each recite “a protein of Gene 32” at the end of the claim. The recitation of “a” protein of Gene 32 encompasses any protein, including fragments, of Gene 32, which is well known in the art as a single stranded DNA binding protein. The specification merely recites "the protein of Gene 32” in lines 1-2 and lines 15-20 of page 6 and in original claims 16 and 18. Lines 10-15 of page 19 of the specification recite “Gene 32 Protein.” In addition, page 19 of the specification only refers to Gene 32 Protein from a specific commercial supplier (Amersham Biosciences). Thus, while the specification supports “the” protein of Gene 32, the broad recitation of “a” protein of Gene 32 encompasses fragments other than the full length protein specifically recited by the specification. Therefore the limitation “a protein of Gene 32” constitutes new matter.

Claim Rejections - 35 USC § 112, Second Paragraph

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 19-41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 19-41 are indefinite in claim 19 (upon which claims 20-32 depend) and claim 33 (upon which claims 34-41 depend), each of which recites the limitation "extending the primer by reading the result of the primer extension" in lines 7-8 of each of claims 19 and 33. The recitation "extending the primer by reading the result of the primer extension" is indefinite because it is unclear how "reading the result" of the primer extension results in "extending the primer" (i.e., extending the primer "by" reading the result). In addition, the recitation of "the primer extension" lacks antecedent basis because the claims do not previously recite a primer extension. It is suggested that the claims be amended to clarify the relationship between reading the result and extending the primer.

B. Claims 32 and 41 contains the trademark/trade names "NP-40," "Tween 20," and "Triton X-100". Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or

product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe specific chemical additives and, accordingly, the identification/description is indefinite.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

9. Claims 19-25, 31, 33-34, and 40 are rejected under 35 U.S.C. 102(a,e) as being anticipated by Quake et al (U.S. Patent Application Publication No. US 2002/0025529 A1, published 28 February 2002, originally filed on 6 November 2000 as U.S. Application No. 09/707,737).

Regarding claim 19, Quake et al teach a method. Quake et al teach providing a single stranded polynucleotide template (i.e., nucleic acid molecule) to which a primer is hybridized (paragraphs 0055 and 0146), thus forming a template/primer complex. A

polymerase and one of the four nucleotide triphosphates are then added (paragraph 0055). The nucleotides in the extension reaction a mixture of labeled and unlabeled nucleotides, wherein the percentage of labeled nucleotides is 19% (i.e., less than 20%; paragraph 0179), which is within the claimed range of 1-50 mole %. The unlabeled nucleotide is the claimed at least one nucleotide, and the labeled nucleotide is the claimed at least one labeled derivative of the at least one nucleotide. The label is attached with a cleavable link (paragraph 0186). The primer is extended via the extension reaction and the result is read; namely, the signal from the label determines the identity of the incorporated nucleotide (paragraph 0014). The label is then removed either by cleaving the cleavable link (paragraph 0186) or by photobleaching (paragraph 0193). The extension step and reading step is then repeated with the next nucleotide mixture (paragraph 0014).

Regarding claims 20-21, Quake et al teach the method of claim 19, wherein the amount of labeled derivative of the at least one nucleotide in said mixture is 19%(i.e., less than 20%; paragraph 0179), which is within the range of 5-50 mole % (i.e., claim 20) and also within the range of 10-50 mole % (i.e., claim 21).

Regarding claim 22, Quake et al teach the method of claim 19, wherein the single stranded form of said nucleic acid molecule is attached to a carrier; namely, the single stranded polynucleotide template is immobilized to the surface of a channel (paragraph 0055).

Regarding claim 23, Quake et al teach the method of claim 22, wherein the mechanism of attachment to the carrier is specific binding to biotin (paragraph 0057).

Regarding claim 24, Quake et al teach the method of claim 23, wherein the carrier is a surface; namely, the surface of a channel (paragraph 0055).

Regarding claim 25, Quake et al teach the method of claim 19, wherein the label is neutralized by photobleaching (paragraph 0193).

Regarding claim 31, Quake et al teach the method of claim 19, wherein the derivative of the nucleotide is a dideoxynucleotide (paragraph 0185).

Regarding claim 33, Quake et al teach a method. Quake et al teach providing a single stranded polynucleotide template (i.e., nucleic acid molecule) to which a primer is hybridized (paragraphs 0055 and 0146), thus forming a template/primer complex. A polymerase and one of the four nucleotide triphosphates are then added (paragraph 0055). The nucleotides in the extension reaction a mixture of labeled and unlabeled nucleotides, wherein the percentage of labeled nucleotides is 19% (i.e., less than 20%; paragraph 0179), which is within the claimed range of 1-50 mole %. The unlabeled nucleotide is the claimed at least one nucleotide, and the labeled nucleotide is the claimed at least one labeled derivative of the at least one nucleotide. The label is attached with a cleavable link (paragraph 0186). The primer is extended via the extension reaction and the result is read; namely, the signal from the label determines the identity of the incorporated nucleotide (paragraph 0014). The label is then removed either by cleaving the cleavable link (paragraph 0186) or by photobleaching (paragraph 0193). The extension step and reading step is then repeated with the next nucleotide mixture (paragraph 0014).

Regarding claim 34, Quake et al teach the method of claim 33, wherein the label is neutralized by photobleaching (paragraph 0193).

Regarding claim 40, Quake et al teach the method of claim 33, wherein the derivative of the nucleotide is a dideoxynucleotide (paragraph 0185).

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 19, 26, 29, 33, 35, and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Quake et al (U.S. Patent Application Publication No. US 2002/0025529 A1, published 28 February 2002, originally filed on 6 November 2000 as U.S. Application No. 09/707,737) in view of Urdea et al (U.S. Patent No. 4,910,300, issued 20 March 1990).

It is noted that this rejection applies to claims 19 and 33 to the extent that they are drawn to the embodiments of dependent claims 26 and 29, and 35 and 38, respectively.

Regarding claims 26 and 29, Quake et al teach the method of claim 19. Quake et al teach providing a single stranded polynucleotide template (i.e., nucleic acid molecule) to which a primer is hybridized (paragraphs 0055 and 0146), thus forming a template/primer complex. A polymerase and one of the four nucleotide triphosphates are then added (paragraph 0055). The nucleotides in the extension reaction a mixture of labeled and unlabeled nucleotides, wherein the percentage of labeled nucleotides is 19% (i.e., less than 20%; paragraph 0179), which is within the claimed range of 1-50 mole %. The unlabeled nucleotide is the claimed at least one nucleotide, and the labeled nucleotide is the claimed at least one labeled derivative of the at least one nucleotide. The label is attached with a cleavable link (paragraph 0186). The primer is extended via the extension reaction and the result is read; namely, the signal from the label determines the identity of the incorporated nucleotide (paragraph 0014). The label is then removed either by cleaving the cleavable link (paragraph 0186) or by

photobleaching (paragraph 0193). The extension step and reading step is then repeated with the next nucleotide mixture (paragraph 0014).

While Quake et al teach the labels are fluorescent labels and that the labels are cleaved via a cleavable linker arm (paragraph 0186), Kawashima et al do not explicitly teach a cleavable link between the label and the nucleotide that is a disulfide (i.e., claim 26) and the linker is shorter than 8 atoms (i.e., claim 29).

However, Urdea et al teach detectably labeled nucleotides (column 8, lines 20-60), wherein the detectable label is a fluorescent label (column 4, lines 5-10) and is linked to the nucleotide with a cleavable linker in the form of a disulfide linker (i.e., claim 26; column 8, lines 20-60). The linker between the disulfide bridge and the base is less than 8 atoms; namely, Formula 13 has label R1, a disulfide for R2, x is one CH2 linker, and NH connects to the base (i.e., claim 29; column 8, lines 20-60). Urdea et al further teach that the nucleotides having the linkers and labels have the added advantage of being inexpensively synthesized in large quantity (column 2, lines 15-40). Thus, Urdea et al teach the known technique of using a disulfide as a cleavable link between a label and a nucleotide.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising the use of labeled nucleotides attached with a cleavable linker as taught by Quake et al so that the cleavable linker is a disulfide linker (i.e., claim 26) that is less than 8 atoms (i.e., claim 29) as taught by Urdea et al to arrive at the instantly claimed method with a reasonable expectation of success. The ordinary artisan would have been motivated to

make the modification because said modification would have resulted in a method having the added advantage of having a decreased cost as a result of utilizing labels that are inexpensively synthesized in large quantity as explicitly taught by Urdea et al (column 2, lines 15-40). In addition, it would have been obvious to the ordinary artisan that the known technique of using the cleavable disulfide linker of Urdea et al could have been applied as the cleavable linker in the method of Quake et al with predictable results because the cleavable disulfide linker of Urdea et al predictably results in a link useful in the labeling of nucleotides.

Regarding claims 35 and 38, Quake et al teach the method of claim 33. Quake et al teach providing a single stranded polynucleotide template (i.e., nucleic acid molecule) to which a primer is hybridized (paragraphs 0055 and 0146), thus forming a template/primer complex. A polymerase and one of the four nucleotide triphosphates are then added (paragraph 0055). The nucleotides in the extension reaction a mixture of labeled and unlabeled nucleotides, wherein the percentage of labeled nucleotides is 19% (i.e., less than 20%; paragraph 0179), which is within the claimed range of 1-50 mole %. The unlabeled nucleotide is the claimed at least one nucleotide, and the labeled nucleotide is the claimed at least one labeled derivative of the at least one nucleotide. The label is attached with a cleavable link (paragraph 0186). The primer is extended via the extension reaction and the result is read; namely, the signal from the label determines the identity of the incorporated nucleotide (paragraph 0014). The label is then removed either by cleaving the cleavable link (paragraph 0186) or by

photobleaching (paragraph 0193). The extension step and reading step is then repeated with the next nucleotide mixture (paragraph 0014).

While Quake et al teach the labels are fluorescent labels and that the labels are cleaved via a cleavable linker arm (paragraph 0186), Kawashima et al do not explicitly teach a cleavable link between the label and the nucleotide that is a disulfide (i.e., claim 35) and the linker is shorter than 8 atoms (i.e., claim 38).

However, Urdea et al teach detectably labeled nucleotides (column 8, lines 20-60), wherein the detectable label is a fluorescent label (column 4, lines 5-10) and is linked to the nucleotide with a cleavable linker in the form of a disulfide linker (i.e., claim 35; column 8, lines 20-60). The linker between the disulfide bridge and the base is less than 8 atoms; namely, Formula 13 has label R1, a disulfide for R2, x is one CH2 linker, and NH connects to the base (i.e., claim 38; column 8, lines 20-60). Urdea et al further teach that the nucleotides having the linkers and labels have the added advantage of being inexpensively synthesized in large quantity (column 2, lines 15-40). Thus, Urdea et al teach the known technique of using a disulfide as a cleavable link between a label and a nucleotide.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising the use of labeled nucleotides attached with a cleavable linker as taught by Quake et al so that the cleavable linker is a disulfide linker (i.e., claim 35) that is less than 8 atoms (i.e., claim 38) as taught by Urdea et al to arrive at the instantly claimed method with a reasonable expectation of success. The ordinary artisan would have been motivated to

make the modification because said modification would have resulted in a method having the added advantage of having a decreased cost as a result of utilizing labels that are inexpensively synthesized in large quantity as explicitly taught by Urdea et al (column 2, lines 15-40). In addition, it would have been obvious to the ordinary artisan that the known technique of using the cleavable disulfide linker of Urdea et al could have been applied as the cleavable linker in the method of Quake et al with predictable results because the cleavable disulfide linker of Urdea et al predictably results in a link useful in the labeling of nucleotides.

13. Claims 27-28 and 36-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Quake et al (U.S. Patent Application Publication No. US 2002/0025529 A1, published 28 February 2002, originally filed on 6 November 2000 as U.S. Application No. 09/707,737) in view of Urdea et al (U.S. Patent No. 4,910,300, issued 20 March 1990) as applied to claims 19, 22, 33, and 35 above, and further in view of Wells et al (J. Biol. Chem., vol. 261, pages 6564-6570 (1986)).

Regarding claims 27-28 and 36-37, the methods of claims 19, 22, 33, and 35 are discussed above in Section 12.

Neither Quake et al nor Urdea teach cleavage is performed by addition of a reducing agent to expose and provide a thiol group (i.e., claims 27 and 36) that is capped by a reagent (i.e., claims 28 and 37).

However, Wells et al teach the disulfides are cleaved with reducing agents to yield free thiol, which are capped by reaction with iodoacetamide to prevent reformation

of disulfides (page 6566, column 1, last paragraph). Thus, Wells et al teach the known technique of reductively cleaving a disulfide to form a thiol group (i.e., claims 27 and 36) that is capped by a reagent (i.e., claims 28 and 37).

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising the use of disulfide linked labeled nucleotides as taught by Quake et al in view of Urdea et al so that the link is reductively cleaved to generate a thiol (i.e., claims 27 and 36) that is capped with a reagent (i.e., claims 28 and 37) as taught by Wells et al to arrive at the instantly claimed method with a reasonable expectation of success. The ordinary artisan would have been motivated to make the modification because said modification would have resulted in a method having the added advantage of preventing the reformation of the disulfides after cleavage as explicitly taught by Wells et al (page 6566, column 1, last paragraph). In addition, it would have been obvious to the ordinary artisan that the known technique of forming and capping an exposed thiol via reduction of a disulfide as taught by Wells et al could have been applied to the method of Quake et al in view of Urdea with predictable results because the known technique of forming and capping an exposed thiol via reduction of a disulfide as taught by Wells et al predictably results in prevention of the reformation of the disulfide link after cleavage.

14. Claims 19, 30, 33, and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Quake et al (U.S. Patent Application Publication No. US 2002/0025529 A1, published 28 February 2002, originally filed on 6 November 2000 as U.S. Application No. 09/707,737) in view of Uemori et al (PCT International Application Publication No. WO 97/24444, published 10 July 1997), as evidenced by Atkins (Physical Chemistry. 3rd Ed., Freeman and Co., New York, 1986, page 278). Citations from Uemori et al are from the National Stage (U.S. Patent No. 6,395,526 B1, issued 28 May 2002). The National Stage is deemed an English language translation of the PCT.

It is noted that this rejection applies to claims 19 and 33 to the extent that they are drawn to the embodiments of dependent claims 30 and 39, respectively.

Regarding claim 30, Quake et al teach the method of claim 19. Quake et al teach providing a single stranded polynucleotide template (i.e., nucleic acid molecule) to which a primer is hybridized (paragraphs 0055 and 0146), thus forming a template/primer complex. A polymerase and one of the four nucleotide triphosphates are then added (paragraph 0055). The nucleotides in the extension reaction a mixture of labeled and unlabeled nucleotides, wherein the percentage of labeled nucleotides is 19% (i.e., less than 20%; paragraph 0179), which is within the claimed range of 1-50 mole %. The unlabeled nucleotide is the claimed at least one nucleotide, and the labeled nucleotide is the claimed at least one labeled derivative of the at least one nucleotide. The label is attached with a cleavable link (paragraph 0186). The primer is extended via the extension reaction and the result is read; namely, the signal from the label determines the identity of the incorporated nucleotide (paragraph 0014). The label

is then removed either by cleaving the cleavable link (paragraph 0186) or by photobleaching (paragraph 0193). The extension step and reading step is then repeated with the next nucleotide mixture (paragraph 0014).

Quake et al teach the cleavage of the linker in step c) is done with mild acid (paragraph 0186). Acidic conditions result in a pH of less than 7, as evidenced by Atkins (page 278). Thus, while Quake et al teach the cleavage portion of step c) is done at a pH below 7, Quake et al does not teach the extension with polymerase occurs at a pH below 7.

However, Uemori et al teach extension reactions of primer template/complexes using a DNA polymerase (Abstract) wherein the polymerase exhibits maximum activity at a pH of 6.5 (column 12, lines 13-16). Uemori et al also teach the DNA polymerase having the activity at pH 6.5 has the added advantage of higher primer extensibility (Abstract) with a lower error rate in DNA synthesis (column 13, lines 30-35), which improves the assay accuracy. Thus, Uemori et al teach the known technique of performing primer extension at a pH below 7.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising the use of a DNA polymerase and cleavage of a linker at a pH below 7 as taught by Quake et al to use the DNA polymerase of Uemori et al to arrive at the instantly claimed method with a reasonable expectation of success. Use of the polymerase of Uemori et al would result in extension reactions performed at a pH 6.5. The ordinary artisan would have been motivated to make the modification because said modification would have resulted

in a method providing the maximum activity of the polymerase and the added advantage of higher primer extensibility with improved assay accuracy as a result of the lower error rate in DNA synthesis of the polymerase as explicitly taught by Uemori et al (Abstract and column 13, lines 30-35). In addition, it would have been obvious to the ordinary artisan that the known technique of using the pH of Uemori et al could have been applied in step c) of the method of Quake et al in with predictable results because the known technique of using the pH of Uemori et al predictably results in a viable primer extension reaction.

Regarding claim 39, Quake et al teach the method of claim 33. Quake et al teach providing a single stranded polynucleotide template (i.e., nucleic acid molecule) to which a primer is hybridized (paragraphs 0055 and 0146), thus forming a template/primer complex. A polymerase and one of the four nucleotide triphosphates are then added (paragraph 0055). The nucleotides in the extension reaction a mixture of labeled and unlabeled nucleotides, wherein the percentage of labeled nucleotides is 19% (i.e., less than 20%; paragraph 0179), which is within the claimed range of 1-50 mole %. The unlabeled nucleotide is the claimed at least one nucleotide, and the labeled nucleotide is the claimed at least one labeled derivative of the at least one nucleotide. The label is attached with a cleavable link (paragraph 0186). The primer is extended via the extension reaction and the result is read; namely, the signal from the label determines the identity of the incorporated nucleotide (paragraph 0014). The label is then removed either by cleaving the cleavable link (paragraph 0186) or by

photobleaching (paragraph 0193). The extension step and reading step is then repeated with the next nucleotide mixture (paragraph 0014).

Quake et al teach the cleavage of the linker in step c) is done with mild acid (paragraph 0186). Acidic conditions result in a pH of less than 7, as evidenced by Atkins (page 278). Thus, while Quake et al teach the cleavage portion of step c) is done at a pH below 7, Quake et al does not teach the extension with polymerase occurs at a pH below 7.

However, Uemori et al teach extension reactions of primer template/complexes using a DNA polymerase (Abstract) wherein the polymerase exhibits maximum activity at a pH of 6.5 (column 12, lines 13-16). Uemori et al also teach the DNA polymerase having the activity at pH 6.5 has the added advantage of higher primer extensibility (Abstract) with a lower error rate in DNA synthesis (column 13, lines 30-35), which improves the assay accuracy. Thus, Uemori et al teach the known technique of performing primer extension at a pH below 7.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising the use of a DNA polymerase and cleavage of a linker at a pH below 7 as taught by Quake et al to use the DNA polymerase of Uemori et al to arrive at the instantly claimed method with a reasonable expectation of success. Use of the polymerase of Uemori et al would result in extension reactions performed at a pH 6.5. The ordinary artisan would have been motivated to make the modification because said modification would have resulted in a method providing the maximum activity of the polymerase and the added

advantage of higher primer extensibility with improved assay accuracy as a result of the lower error rate in DNA synthesis of the polymerase as explicitly taught by Uemori et al (Abstract and column 13, lines 30-35). In addition, it would have been obvious to the ordinary artisan that the known technique of using the pH of Uemori et al could have been applied in step c) of the method of Quake et al in with predictable results because the known technique of using the pH of Uemori et al predictably results in a viable primer extension reaction.

15. Claims 19, 32, 33, and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Quake et al (U.S. Patent Application Publication No. US 2002/0025529 A1, published 28 February 2002, originally filed on 6 November 2000 as U.S. Application No. 09/707,737) in view of Hyman (U.S. Patent No. 5,516,664, issued 14 May 1996).

It is noted that this rejection applies to claims 19 and 33 to the extent that they are drawn to the embodiments of dependent claims 32 and 41, respectively.

Regarding claim 32, Quake et al teach the method of claim 19. Quake et al teach providing a single stranded polynucleotide template (i.e., nucleic acid molecule) to which a primer is hybridized (paragraphs 0055 and 0146), thus forming a template/primer complex. A polymerase and one of the four nucleotide triphosphates are then added (paragraph 0055). The nucleotides in the extension reaction a mixture of labeled and unlabeled nucleotides, wherein the percentage of labeled nucleotides is 19% (i.e., less than 20%; paragraph 0179), which is within the claimed range of 1-50

mole %. The unlabeled nucleotide is the claimed at least one nucleotide, and the labeled nucleotide is the claimed at least one labeled derivative of the at least one nucleotide. The label is attached with a cleavable link (paragraph 0186). The primer is extended via the extension reaction and the result is read; namely, the signal from the label determines the identity of the incorporated nucleotide (paragraph 0014). The label is then removed either by cleaving the cleavable link (paragraph 0186) or by photobleaching (paragraph 0193). The extension step and reading step is then repeated with the next nucleotide mixture (paragraph 0014).

While Quake et al teach a label that is cleaved (paragraph 0186), Quake et al do not teach a functionally equivalent label is cleaved using an agent in the form of alkaline phosphatase.

However, Hymen teaches the extension of a primer using a functionally equivalent blocked nucleotide, wherein the blocking group is removed with an agent in the form of a phosphatase (Abstract); namely, alkaline phosphatase (Example 5). Thus, Hyman teaches the known technique of extending a nucleic acid with a label that is removed using an agent in the form of alkaline phosphatase.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method of Quake et al so that the blocking label is the functionally equivalent label that is cleaved using an agent in the form of alkaline phosphatase as taught by Hyman to arrive a the instantly claimed method with a reasonable expectation of success. It would have been obvious to the ordinary artisan that the known technique of using the functionally equivalent label that

is cleaved using an agent in the form of alkaline phosphatase as taught by Hyman could have been applied as the label in the method of Quake et al in with predictable results because the known technique of using the functionally equivalent label that is cleaved using an agent in the form of alkaline phosphatase as taught by Hyman predictably results in a functionally equivalent label for blocking a primer extension reaction.

Regarding claim 41, Quake et al teach the method of claim 33. Quake et al teach providing a single stranded polynucleotide template (i.e., nucleic acid molecule) to which a primer is hybridized (paragraphs 0055 and 0146), thus forming a template/primer complex. A polymerase and one of the four nucleotide triphosphates are then added (paragraph 0055). The nucleotides in the extension reaction a mixture of labeled and unlabeled nucleotides, wherein the percentage of labeled nucleotides is 19% (i.e., less than 20%; paragraph 0179), which is within the claimed range of 1-50 mole %. The unlabeled nucleotide is the claimed at least one nucleotide, and the labeled nucleotide is the claimed at least one labeled derivative of the at least one nucleotide. The label is attached with a cleavable link (paragraph 0186). The primer is extended via the extension reaction and the result is read; namely, the signal from the label determines the identity of the incorporated nucleotide (paragraph 0014). The label is then removed either by cleaving the cleavable link (paragraph 0186) or by photobleaching (paragraph 0193). The extension step and reading step is then repeated with the next nucleotide mixture (paragraph 0014).

While Quake et al teach a label that is cleaved (paragraph 0186), Quake et al do not teach a functionally equivalent label is cleaved using an agent in the form of alkaline phosphatase.

However, Hymen teaches the extension of a primer using a functionally equivalent blocked nucleotide, wherein the blocking group is removed with an agent in the form of a phosphatase (Abstract); namely, alkaline phosphatase (Example 5). Thus, Hyman teaches the known technique of extending a nucleic acid with a label that is removed using an agent in the form of alkaline phosphatase.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method of Quake et al so that the blocking label is the functionally equivalent label that is cleaved using an agent in the form of alkaline phosphatase as taught by Hyman to arrive a the instantly claimed method with a reasonable expectation of success. It would have been obvious to the ordinary artisan that the known technique of using the functionally equivalent label that is cleaved using an agent in the form of alkaline phosphatase as taught by Hyman could have been applied as the label in the method of Quake et al in with predictable results because the known technique of using the functionally equivalent label that is cleaved using an agent in the form of alkaline phosphatase as taught by Hyman predictably results in a functionally equivalent label for blocking a primer extension reaction.

Response to Arguments

16. Applicant's arguments filed 3 June 2008, the identical supplemental arguments filed 19 June 2008, and the arguments filed 29 September 2008 all refer to the previous rejections of the claims. All of Applicant's arguments with respect to the previous rejections of the claims have been considered but are moot in view of the new ground(s) of rejection necessitated by the amendments.

Conclusion

17. No claim is allowed.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert T. Crow whose telephone number is (571)272-1113. The examiner can normally be reached on Monday through Friday from 8:00 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Robert T. Crow/
Examiner, Art Unit 1634

Robert T. Crow
Examiner
Art Unit 1634